

**REMARKS**

Claims 15-16 and 19-23 are pending and under consideration. Claim 15 is currently amended with support found throughout the specification, *i.e.*, page 8 lines 15-25. No new matter is added by this amendment.

**Rejection under 35 U.S.C. § 103(a)**

Claims 15-16 and 19-23 are rejected as allegedly being unpatentable over either JP 08 231417 ("JP417") or Maitani (J. of Pharmaceutical Sciences, 1996) ("Maitani") by themselves or in view of U.S. Patent No. 5,874,075 ("Collins") further in view of JP 61097229 ("JP229"). Applicant and Applicant's representatives ("Applicant") respectfully traverse.

**Relevant Case Law**

In levying an obviousness rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing that the prior art reference teaches or suggests all of the claim limitations. M.P.E.P. §2143; *see also*, *In re Royka*, 490 F.2d 981 (CCPA 1974). To determine obviousness, Examiners must consider (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the pertinent art, and (4) objective evidence relevant to the issue of obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). In addition, the Supreme Court has pointed out the "import[ance] to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (U.S. 2007). The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic.

*In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). Applicants submit that the cited art do not provide the necessary teaching, expressly or inherently, for one of ordinary skill in the art to make the claimed invention.

*Analysis of Invention versus the Cited Art*

The present invention requires at least the following as cited in base claim 15:

A liposomal-based parenteral composition comprising:

- (a) an aqueous phase comprising an aqueous buffer solution;
- (b) a lipidic phase comprising single bilayered liposomes dispersed within the aqueous phase, wherein said lipidic phase is not a product of reverse-phase evaporation;
- (c) an effective amount of an active ingredient comprising erythropoietin or its pharmaceutically acceptable derivatives having the biological properties of causing bone marrow cells to increase production of reticulocytes and red blood cells, said active ingredient being dispersed within the aqueous phase; and
- (d) glycine, said glycine being dispersed within the aqueous phase.

*Analysis of JP417*

JP417 does not teach or suggest, alone or in combination, the presently claimed invention. In fact, JP417 requires the use of reverse-phase evaporation in the preparation of the JP417 composition. Reverse-phase evaporation is known and used in the art to drive encapsulation of compounds such as erythropoietin ("EPO"). The presently claimed invention does not claim this technique or products by this technique. In fact, the present invention specifically does not permit liposomes in the lipidic phase that are products of the reverse-phase evaporation technique as required in JP417.

JP417 does not teach a composition with the active ingredient comprising EPO, wherein the EPO is dispersed in the aqueous phase external to the liposome. In fact, the Examiner admits on the record that non-encapsulated EPO is removed by filtration. Therefore, JP417 does not teach a composition as presently claimed. The composition of JP417 fully encapsulates the EPO. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to not remove the compound. Office Action at Page 3. This allegation is baseless and without merit in the face of the cited art. The Examiner provided no rationale or analysis for this allegation and provided no art to support why one of ordinary skill in the art would look to this reference for a teaching or suggestion to leave non-encapsulated EPO in the composition. At best, the Examiner has used hindsight analysis in this regard. Therefore, the allegation should be withdrawn.

Additionally, the Examiner admits at page 3 of the Office Action that JP417 does not teach the use of glycine in the JP417 composition. Therefore, JP417 cannot stand alone as alleged by the Examiner because JP417 does not teach all the requirements of the claimed invention. Office Action at Page 2.

In conclusion, the Applicant has shown that JP417 requires reverse-phase evaporation and the composition of JP417 fully encapsulates the EPO, because the non-encapsulated EPO is removed as acknowledged by the Examiner. Moreover, the Examiner provided no rationale or merit based analysis as to why one of ordinary skill in the art would rely on JP417 as a teaching or suggestion for not removing the non-encapsulated EPO. Removal of non-encapsulated EPO is an objective of the cited art; therefore, JP417 actually teaches away from a composition with the EPO being dispersed in the aqueous phase. Finally, JP417 fails to discuss any composition using

glycine dispersed in the aqueous phase, and therefore cannot stand as a “stand alone” reference as asserted by the Examiner.

*Analysis of Maitani*

Maitani does not teach or suggest, alone or in combination, the presently claimed invention. Maitani does not remedy the deficiencies of JP417, nor is Maitani combinable with JP417 to teach or suggest the presently claimed invention. In fact, Maitani suffers the same deficiencies of JP417.

Maitani teaches an oral composition of liposome encapsulated EPO as products of a reverse-phase evaporation technique, wherein the non-encapsulated EPO is removed via evaporation as stated by the Examiner at page 3 of the Office Action. Although the Examiner states that it would have been obvious to one of ordinary skill in the art to leave the EPO in the aqueous phase, neither the cited nor the Examiner offered any rationale, teaching or suggestion as to why one of ordinary skill in the art would do so. As with JP417, Maitani teaches away from leaving the EPO in the aqueous phase because Maitani and JP417 need the EPO encapsulated for absorption across the digestive system. Therefore, there is no rationale as to why one of ordinary skill in the art would be motivated to go against the teachings of Maitani and JP417. In fact, Maitani uses only liposomal-encapsulated EPO as products of reverse-phase evaporation in the absence of EPO in the aqueous phase. Moreover, Maitani espouses absorption of the liposomal-encapsulated EPO through oral administration. For at least these reasons, Maitani is teaching away from the present invention wherein the EPO is dispersed in the aqueous phase external to the liposome. Moreover, there is no teaching or suggestion for one of ordinary

skill to completely go against Maitani to form the currently claimed parenteral composition wherein the EPO, as part of the active ingredient, is dispersed in the aqueous phase.

Additionally, Maitani does not teach or suggest the use of glycine as dispersed in the aqueous phase. In fact, the Examiner admits this on page 3 of the Office Action. Therefore, Maitani fails to teach or suggest each and every requirement of the present invention, and cannot serve as a “stand alone reference” for a *prima facie* case of obviousness as alleged by the Examiner on page 2 of the Office Action.

In conclusion, the Applicant has shown that Maitani requires reverse-phase evaporation and the composition of Maitani fully encapsulates the EPO, because the non-encapsulated EPO is removed as stated by the Examiner. Moreover, the Examiner provided no rationale or merit based analysis as to why one of ordinary skill in the art would rely on Maitani as teaching or suggesting not removing the non-encapsulated EPO. Maitani teaches removal of non-encapsulated EPO; therefore, Maitani actually teaches away from a composition with the EPO being in the aqueous phase. Furthermore, Maitani is drawn to oral liposomal/EPO encapsulation for oral administration in an attempt to improve absorption across the digestive tract. Conversely, the present invention is to a parenteral injection of a liposomal lipidic phase, and an aqueous phase with EPO dispersed therein. Finally, Maitani fails to discuss any composition using glycine dispersed in the aqueous phase, and therefore cannot be applied as a “stand alone” reference as asserted by the Examiner.

Analysis of Collins

Collins does not teach or suggest, alone or in combination, the presently claimed liposomal-based parenteral composition having a lipidic phase and an aqueous phase with EPO dispersed in the aqueous phase. Collins does not remedy any or all the deficiencies of JP417 and/or Maitani.

Collins requires compounds be attached to the liposomes. Collins does not provide any teaching or suggestion for one of ordinary skill in the art to make the presently claimed invention wherein the EPO is dispersed in the aqueous phase. Again, Collins focuses on liposomal attachment of compounds for oral administration. This is neither taught nor claimed in the present invention. Furthermore, EPO is part of a larger genus in Collins without any examples, guidance or specificity as to how it would be accomplished or to what effect. In fact, Collins does not teach a specific compound where the EPO is dispersed in the aqueous phase. To this point, the Examiner alleges that it would be implicit that EPO would be dispersed in the aqueous phase. Office Action at Page 4. This is a baseless assertion without any rationale. Collins does not provide any teaching or suggestion as to the existence of the Examiner's claim of "implicit" existence of EPO in the aqueous phase. Again, Collins is largely silent regarding EPO, and does not provide a sufficient basis for a *prima facie* case of obvious, alone or in combination, regarding EPO. Simply stated, one of ordinary skill in the art would not look to Collins as a source for making the presently claimed invention. The fact that EPO is mentioned in a genus group without any guidance, examples or specificity does not provide teaching or suggestion to

one of ordinary skill in the art as to making the presently claimed invention. The nexus is far to tenuous.

In conclusion, the Applicant has shown that Collins requires liposomal attachment of the compounds disclosed therein. Collins only discusses EPO by partial similarity, but more importantly only mentions EPO as part of a larger genus. Collins does not provide any teaching in the form of examples, guidance or specificity regarding the use of EPO as part of the liposomal attachment. Collins simply does not provide any basis for one of ordinary skill in the art to make the presently claimed invention. Collins does not remedy any deficiencies of JP417 or Maitani, and Collins provides even more deficiencies for one of ordinary skill in the art to overcome in order to make the presently claimed invention. Finally, Maitani fails to discuss any composition using glycine dispersed in the aqueous phase. For at least these reasons and the reasons stated for Maitani and JP417, Collins cannot serve, alone or in part, as the basis of a *prima facie* case of obviousness.

Analysis of JP229

JP229 does not teach or suggest, alone or in combination, the presently claimed invention. JP229 does not remedy any deficiencies of JP417, Maitani or Collins. JP229 does not teach liposomes. The Examiner, however, only relies on JP229 for teaching glycine as a stabilizer. To this point, the Examiner asserts that stability of the presently claimed invention could be solely based on the addition of glycine. Office Action at Page 4-5. Contrary to the Examiner's assertion, the presently disclosed liposomes are stable within themselves. Applicant, however, wishes to direct the Examiner's attention to the Specification, page 7, lines 18-21,

wherein the invention as disclosed can use the addition of glycine regarding formations of aggregates as an additional stabilizer, if desired. Therefore, the Examiner's assertion is unsubstantiated regarding the stability of the liposomes being due solely to the glycine.

For at least these reasons and those stated *supra*, JP229 does not provide the requisite teachings or suggestion for one of ordinary skill in the art to make the presently claimed invention. Moreover, due to the deficiencies of JP417, Maitani and Collins, JP229 does not complete the necessary teaching and suggestion for making the presently claimed invention.

### **Conclusion**

For the reasons discussed *supra*, the cited references do not complete a *prima facie* case of obviousness regarding the presently claimed liposomal-based parenteral composition wherein the active ingredient comprising EPO is dispersed in the aqueous phase, and wherein the lipidic phase comprises a stable, single bilayered liposome dispersed in the aqueous phase, wherein the liposome is not a product of reverse phase evaporation technique. Therefore, Applicant respectfully requests that the Examiner withdraw the rejections and move the application to allowance.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicants submit concurrently a request for a two-month extension of time under 37 C.F.R. § 1.136 and the accompanying fee. Applicant also submits concurrently a Request for Continued Examination pursuant to 37 C.F.R. § 1.114. Please charge our Credit Card in the amount of \$1300.00 covering the fees set forth in 37 C.F.R. § 1.17(e) and 1.17(a)(3). In the

event that any additional extensions of time are necessary to prevent the abandonment of this patent application, then such extensions of time are petitioned. The U.S. Patent and Trademark Office is authorized to charge any additional fees that may be required in conjunction with this submission to Deposit Account No. 50-2228, under 026038.0240N1US from which the undersigned is authorized to draw.

Dated: February 24, 2010

Respectfully submitted,

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